

position. In accordance with the requirements of 37 C.F.R. § 1.101, a marked up version of the claims showing the changes is attached as Appendix A. For the Examiner's convenience, a complete set of the currently pending claims is also provided as Appendix B.

**Sequence Listing:**

Add the enclosed Sequence Listing to the application.

**REMARKS**

**Status of the Claims.**

Claims 1-58 were pending in the present application. Claims 24-50 were withdrawn from consideration pursuant to a restriction requirement and have been cancelled. Claims 1-5, 7, 8, 10, 12-19, 22, 23, 51, 53-58 have been amended, and claims 59-64 have been added. Accordingly, Claims 1-23 and 51-64 are pending after entry of the above amendments.

Support for the amendments is as follows. The claims have been amended to even more clearly recite the invention, to ensure consistent use of terminology throughout the claims, and to correct informalities. Support for the amendment to claims 2(2), 3(7), 18(2), and 51(2) is found in the specification at least at page 6, line 29 to page 7, line 3; page 23, lines 1-3; page 25, lines 4-13; and page 34, lines 20-23. Support for the amendments to claims 7 and 54 is found at least at page 28, lines 11-21. The amendments to claims 14 and 16 find support at least in original claims 5 and 6. Support for the amendments to claims 19 and 55 is found in the specification at least at page 37, lines 9-11. The amendments to claim 56 and added claim 63 find support at least at page 38, line 25 to page 39, line 3. Added claim 59 finds support at page 22, lines 9-16. Added claim 60 finds support at page 21, line 25 to page 22, line 3. Added claim 61 finds support in original claim 2; and added claim 62 finds support in original claim 3.

**Election/Restriction.**

Pursuant to a restriction requirement made final, Applicants have canceled claims 24-50. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and that the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Claims 51-58 were added in an Amendment filed in response to the restriction requirement. In the outstanding Office Action, the Examiner alleged that these claims were drawn to a nonelected invention and therefore withdrew claims 51-58 from consideration. Office Action, at page 2. The withdrawal of these claims from consideration is respectfully traversed. The only explanation for this action was the Examiner's statement that "[c]laims 51-58 are drawn to a method for obtaining an optimized recombinant cell-specific binding moiety **polypeptide** useful for increasing uptake, efficacy, or specificity of a vaccine antigen by a target cell." *Id.* (emphasis original).

It is unclear how the term "polypeptide" in the preamble of claim 51 justifies withdrawal from consideration. A comparison of claim 51 with claim 18 (which is drawn to the elected invention) shows that both claims relate to producing and screening recombinant cell-specific binding moiety polypeptides. *See, e.g.,* claim 18(4) and claim 51(4) which recite identical language.

Accordingly, Applicants submit that claims 51-58 are drawn to the elected invention and should be examined in the present application. Consideration of these claims is therefore respectfully requested. To facilitate such consideration, the following remarks explain why claims 51-58 are free of the outstanding rejections, in addition to discussing the rejected claims. If, in light of the foregoing, the Examiner still believes that claims 51-58 are drawn to a non-elected invention, an Examiner Interview is respectfully requested.

**35 U.S.C. § 112, Second Paragraph.**

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Office Action, at page 3. The rejection is respectfully traversed.

The Examiner contends that the phrase "a further form of the polynucleotide that encodes a nucleic acid binding domain and/or a further form of the polynucleotide that encodes a cell-specific ligand" renders claim 3 indefinite. The Examiner stated: "It is unclear what is intended by the claimed invention, a polynucleotide that encodes a nucleic acid binding domain or a polynucleotide that encodes a cell-specific ligand, or both?" Office Action, at page 3. Evidently, the Examiner is confused by the term "and/or," which is standardly used between two items, e.g., item A and item B, to indicate three possibilities: (1) item A, (2) item B, or (3) items A and B together. The Examiner identified these three possibilities, and then apparently determined that the claim could only recite one of these possibilities and that the claim was unclear with respect to which possibility was recited.

Applicants submit that nothing in the phrase quoted above would lead those of skill in the art to interpret the claim in this manner. Rather those of skill would readily appreciate that the above-quoted phrase encompasses embodiments of the method employing: (1) “a further form of the polynucleotide that encodes a nucleic acid binding domain” *or* (2) “a further form of the polynucleotide that encodes a cell-specific ligand” *or* (3) both further forms together. As indicated in M.P.E.P. § 2173.05(h), alternative expressions are permitted in claims. Therefore, Applicants submit that claim 3 is clear and definite and respectfully request withdrawal of the rejection.

**35 U.S.C. § 112, First Paragraph.**

Claims 1-23 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that “the specification, while being enabling for methods disclosed by Ledley et al., 1994 (AH), Patten et al., 1997(BG) and Stemmer et al. 1997 (AG), . . . [which employ] iterative selection and recombination . . . , does not reasonably provide enablement for a method for obtaining a cell-specific binding molecule useful for increasing uptake or specificity of a genetic vaccine to a target cell . . . by any method other than the iterative selection and recombination as discussed above.” Office Action, at page 4. The rejection is respectfully traversed.

The rejected claims include method claims 1-13 and 18-23 as well as composition claims 14-17. Claims 1, 2, and 18 are independent claims reciting methods that entail recombining at least two nucleic acids. Claim 22 recites a method for producing a composition for eliciting an immune response that includes “coating a polynucleotide that is capable of expressing an antigen with a recombinant cell-specific binding moiety produced by the method of claim 18.” The remaining rejected method claims depend, directly or indirectly, from claims 2 or 18. Composition claims 14-17 relate to a cell-specific binding moiety (claim 14) and compositions for eliciting an immune response that include such a moiety (claims 15 and 17) or include a recombinant binding moiety-encoding nucleic acid (claim 16).

The Examiner’s contention that the specification does not enable the use of methods other than the iterative recombination and selection methods described in Ledley, Patten, and Stemmer is apparently intended to support the rejection of the method claims including a recombination step, i.e., claims 1, 2, and 18, as well as the claims depending therefrom. In describing the recombination step, Applicants’ specification indicates that

“[i]n a presently preferred embodiment, the recombinant libraries are prepared using DNA shuffling” (page 20, lines 12-26) and then goes on to state:

Exemplary formats and examples for sequence recombination, sometimes referred to as DNA shuffling, evolution, or molecular breeding, have been described by the present inventors and co-workers in co-pending applications U.S. Patent Application Serial No. 08/198,431, filed February 17, 1994, Serial No. PCT/US95/02126, filed, February 17, 1995, Serial No. 08/425,684, filed April 18, 1995, Serial No. 08/537,874, filed October 30, 1995, Serial No. 08/564,955, filed November 30, 1995, Serial No. 08/621,859, filed March 25, 1996, Serial No. 08/621,430, filed March 25, 1996, Serial No. PCT/US96/05480, filed April 18, 1996, Serial No. 08/650,400, filed May 20, 1996, Serial No. 08/675,502, filed July 3, 1996, Serial No. 08/721, 824, filed September 27, 1996, Serial No. PCT/US97/17300, filed September 26, 1997, and Serial No. PCT/US97/24239, filed December 17, 1997; Stemmer, *Science* 270:1510 (1995); Stemmer et al., *Gene* 164:49-53 (1995); Stemmer, *Bio/Technology* 13:549-553 (1995); Stemmer, *Proc. Natl. Acad. Sci. U.S.A.* 91:10747-10751 (1994); Stemmer, *Nature* 370:389-391 (1994); Cramer et al., *Nature Medicine* 2(1):1-3 (1996); Cramer et al., *Nature Biotechnology* 14:315-319 (1996), each of which is incorporated by reference in its entirety for all purposes.

Other methods for obtaining recombinant polynucleotides and/or for obtaining diversity in nucleic acids used as the substrates for DNA shuffling include, for example, homologous recombination (PCT/US98/05223; Publ. No. WO98/42727); oligonucleotide-directed mutagenesis (for review see, Smith, *Ann. Rev. Genet.* 19: 423-462 (1985); Botstein and Shortle, *Science* 229: 1193-1201 (1985); Carter, *Biochem. J.* 237: 1-7 (1986); Kunkel, “The efficiency of oligonucleotide directed mutagenesis” in *Nucleic acids & Molecular Biology*, Eckstein and Lilley, eds., Springer Verlag, Berlin (1987)). Included among these methods are oligonucleotide-directed mutagenesis (Zoller and Smith, *Nucl. Acids Res.* 10: 6487-6500 (1982), *Methods in Enzymol.* 100: 468-500 (1983), and *Methods in Enzymol.* 154: 329-350 (1987)) phosphothioate-modified DNA mutagenesis (Taylor et al., *Nucl. Acids Res.* 13: 8749-8764 (1985); Taylor et al., *Nucl. Acids Res.* 13: 8765-8787 (1985); Nakamaye and Eckstein, *Nucl. Acids Res.* 14: 9679-9698 (1986); Sayers et al., *Nucl. Acids Res.* 16: 791-802 (1988); Sayers et al., *Nucl. Acids Res.* 16: 803-814 (1988)), mutagenesis using uracil-containing templates (Kunkel, *Proc. Nat'l. Acad. Sci. USA* 82: 488-492 (1985) and Kunkel et al., *Methods in Enzymol.* 154: 367-382); mutagenesis using gapped duplex DNA (Kramer et al., *Nucl. Acids Res.* 12: 9441-9456 (1984); Kramer and Fritz, *Methods in Enzymol.* 154: 350-367 (1987); Kramer et al.,

Nucl. Acids Res. 16: 7207 (1988)); and Fritz et al., Nucl. Acids Res. 16: 6987-6999 (1988)). Additional suitable methods include point mismatch repair (Kramer et al., Cell 38: 879-887 (1984)), mutagenesis using repair-deficient host strains (Carter et al., Nucl. Acids Res. 13: 4431-4443 (1985); Carter, Methods in Enzymol. 154: 382-403 (1987)), deletion mutagenesis (Eghtedarzadeh and Henikoff, Nucl. Acids Res. 14: 5115 (1986)), restriction-selection and restriction-purification (Wells et al., Phil. Trans. R. Soc. Lond. A 317: 415-423 (1986)), mutagenesis by total gene synthesis (Nambiar et al., Science 223: 1299-1301 (1984); Sakamar and Khorana, Nucl. Acids Res. 14: 6361-6372 (1988); Wells et al., Gene 34: 315-323 (1985); and Grundström et al., Nucl. Acids Res. 13: 3305-3316 (1985). Kits for mutagenesis are commercially available (e.g., Bio-Rad, Amersham International, Anglian Biotechnology).

Applicants' specification, at page 20, line 27 to page 21, line 23. Applicants' specification also teaches that "diversity resulting from recombination can be augmented in any cycle by applying prior methods of mutagenesis (e.g., error-prone PCR or cassette mutagenesis) to either the substrates or products for recombination." Applicants' specification, at page 19, lines 22-24. Thus, Applicants' specification cites a wide variety of conventional techniques that can be employed to obtain recombinant polynucleotides suitable for use in the claimed methods.

In an effort to establish a *prima facie* case of non-enablement, the Examiner cited passages from Stemmer relating to the limitations of error-prone PCR and cassette mutagenesis, which the Examiner apparently believes precludes their use in obtaining recombinant polynucleotides. Office Action, at page 5. The cited passages appear in Stemmer (Publication No. WO 97/20078) at page 3, lines 3-35. In citing from this section of the application, the Examiner overlooked the immediately preceding passage, which states that "[e]rror-prone PCR and oligonucleotide-directed mutagenesis are thus useful for single cycles of sequence fine tuning but rapidly become limiting when applied for multiple cycles." Stemmer, at page 3, lines 3-6. The passage immediately following the section cited by the Examiner states:

Error-prone PCR and cassette mutagenesis are thus best suited and have been widely used for fine-tuning areas of comparatively low information content. An example is the selection of an RNA ligase ribozyme from a random library using many rounds of amplification by error-prone PCR and selection . . . .

Stemmer, at page 3, line 36 to page 4, line 4. Far from suggesting that error-prone PCR and cassette mutagenesis are not useful for producing recombinant polypeptides, Stemmer explicitly states that these techniques are useful for some applications. That error-prone PCR and cassette mutagenesis may not be the preferred techniques for use in methods involving multiple cycles of recombination and screening is irrelevant to the enablement inquiry. Applicants respectfully point out that only claim 3 requires more than one cycle of recombination and screening. Furthermore, as Stemmer indicates, there is sufficient experience with error-prone PCR and cassette mutagenesis that one of skill in the art could select an appropriate recombination technique for use in a particular application. *See, e.g.*, Stemmer, at page 2, line 5 to page 4, line 4. Accordingly, Applicants submit that the Examiner's reliance on Stemmer to establish lack of enablement of the claimed methods is misplaced.

The Examiner also expressed the view that "the specification . . . fails to proved enabling disclosure for any genetic vaccine containing the cell-specific binding moiety produced by the claimed invention which stimulates [an] immune response in a host and shows protection of said host from a particular disease or disorder." Office Action, at page 6. Without agreeing with this view, Applicants respectfully point out that none of the previously or currently pending claims requires that a genetic vaccine stimulate an protective immune response. As 34 U.S.C. § 112 requires only that the specification and the *claimed* invention be commensurate in scope, Applicants submit that questions regarding the ability of genetic vaccines to confer protective immunity are irrelevant to determining enablement.

The Examiner further urged that:

In view of the problems set forth above for the error-prone PCR and cassette mutagenesis, it is unclear whether the claimed invention could provide a cell-specific binding moiety having increased uptake or specificity of a genetic vaccine for a target cell

Office Action, at page 6. As explained above the limitations of error-prone PCR and cassette mutagenesis affect whether these techniques would be used in particular applications of the claimed methods. However, the Examiner has failed to establish how such limitations cast doubt on the ability to obtain a cell-specific binding moiety capable of improving the uptake or specificity of a genetic vaccine.

Furthermore, the claims do not require the invention to provide "a cell-specific binding moiety having increased uptake or specificity" in all instances, although such moieties are certainly within the scope of the pending claims. Independent method

claims 1, 2, and 18 all recite “a method for producing and *screening* a . . . cell-specific binding” molecule (claim 1) or moiety (claims 2 and 18) “for an ability to increase uptake or specificity of a genetic vaccine.” (Emphasis added.) As stated above, method claim 22 relates to coating “a recombinant cell-specific binding moiety produced by the method of claim 18” onto a polynucleotide that is capable of expressing an antigen. These claims contain no requirement that the cell-specific binding moiety have increased uptake or specificity, and no such requirement is found in any of the other method claims, which depend (directly or indirectly) from claims 2 or 18. Composition claims 14-17 are similarly devoid of any requirement that the recombinant cell-specific binding moiety have enhanced uptake or specificity.

In view of the foregoing, none of the grounds for the § 112, first paragraph, rejection is sufficient to establish a *prima facie* case of lack of enablement. Applicants submit that claims 1-23 are appropriately tailored to the disclosure in the specification and, therefore, respectfully request withdrawal of the § 112, first paragraph, rejection. Applicants further submit that claims 51-58, which were not examined (but which should have been), also satisfy the requirements of § 112, first paragraph for at least the reasons discussed above. The same is true of claims 59-64, which were added in this Amendment and which each depend from one of the above-discussed claims.

### **35 U.S.C. § 103(a).**

Claims 1-23 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Stemmer et al. (WO97/20078) in view of Ledley et al. (WO94/25608) and Patten et al. (Current Opinion in Biotechnology (1997) 8:724-733). Office Action, at page 7. This rejection is respectfully traversed.

The three elements of a *prima facie* case of obviousness are: (1) the reference(s) must teach or suggest all of the elements of the claimed invention, (2) there must be some motivation for combining or modifying the teachings of the references to arrive at the claimed invention, and (3) the reference(s) or knowledge in the art must provide a reasonable expectation of success, i.e., a reasonable assurance that the claimed invention would work.

In explaining the rejection, the Examiner stated that “Stemmer teaches a method for the production of nucleic acid fragments or polynucleotides encoding mutant proteins by repeated cycles of mutagenesis, shuffling and selection of nucleic acids to generate polynucleotides having desired characteristic [*sic*] by iterative selection and

recombination for the molecular evolution *in vitro* or *in vivo* of proteins (e.g. abstract).”

Office Action, at page 8. The Examiner noted that “Stemmer does not teach generating a chimeric recombinant DNA comprising a DNA binding domain and a ligand which binds to the surface of a target cell.” Office Action, at page 9.

The Examiner cites Ledley as teaching “generating a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA.” Office Action, at page 9. The Examiner also notes that Ledley teaches “a complex for gene transfer comprising a DNA molecule specifically and non-specifically bound to the chimeric recombinant DNA-binding protein (e.g. p. 26, 27, abstract).” *Id.*

Finally, the Examiner cites Patten’s statement that “viral vaccine vectors can be enhanced by DNA shuffling to give desired properties of tropism, stability and expression level” as well as Patten’s reference to “opportunities for DNA shuffling as a tool for increasing the efficiency and success rate of the development of novel whole organism, viral, bacterial and recombinant protein vaccines.” Patten, at page 732; *see* Office Action, at page 9.

Distinctions over the cited references are described below for each rejected independent claim. In the interest of brevity, the following remarks focus on the Ledley and Patten references because the Examiner relied on these references as teaching the application of the Stemmer methods to vaccines. *See* Office Action, at page 9. The Examiner will, of course, appreciate that Applicants’ remarks relate to the cited combination of references over which the claims were rejected. Simply dismissing Applicants’ arguments as directed to the references individually would therefore be inappropriate. If the Examiner disagrees on this point, an Examiner Interview is respectfully requested.

### **Claim 1**

Claim 1 relates to a “method for producing and screening a cell-specific binding molecule for an ability to increase uptake or specificity of a genetic vaccine for a target cell.” Claim 1 recites:

creating a library of recombinant polynucleotides by  
recombining at least one nucleic acid that encodes a  
polypeptide that comprises a nucleic acid binding domain and  
at least one nucleic acid that encodes a polypeptide that  
comprises a cell-specific binding domain.

As noted above, the Examiner relies on Ledley as teaching this element of claim 1. Ledley teaches “a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA.” Ledley, at page 13, line 35 to page 14, line 1. Suitable first elements are described in Ledley at page 14, line 35 to page 15, line 24. Ledley contains general disclosures regarding how the disclosed chimeric proteins are produced. See page 10, lines 7-18 and page 16, lines 5-7.

Ledley does not, however, teach or suggest “creating a library of recombinant polynucleotides” by recombining a nucleic acid encoding one desired function, such as a nucleic acid binding domain, with another nucleic acid encoding a different desired function, such as a cell-specific binding domain. Nor can this teaching be found in Patten.

### Claim 2

Claim 2 relates to a “method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake or specificity of a genetic vaccine for a target cell. Claim 2 recites:

***recombining*** at least first and second forms of at least one nucleic acid which comprises ***a polynucleotide that encodes a nucleic acid binding domain*** and at least first and second forms of at least one nucleic acid which comprises ***a polynucleotide that encodes a cell-specific ligand*** that specifically binds to a protein on the surface of a cell of interest, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant binding moiety-encoding nucleic acids.

(Emphasis added.) Claim 2, like claim 1, entails recombining a nucleic acid encoding one desired function, such as a nucleic acid binding domain, with another nucleic acid encoding a different desired function, such as a cell-specific binding domain. (In claim 2, two forms of each type of nucleic acid are recombined “to produce a library of recombinant binding moiety-encoding nucleic acids.”) Thus, claim 2 is distinguished from the cited references for the reasons discussed above for claim 1.

An additional distinction is that claim 2 recites:

introducing into one or more host cells one or more members of ***a library of vectors, each of which comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the library of recombinant binding moiety-encoding nucleic acids***, wherein the encoded recombinant binding moiety is expressed.

(Emphasis added.) As noted above, the library of recombinant binding moiety-encoding nucleic acids is produced from “at least first and second forms of at least one nucleic acid which comprises a polynucleotide that encodes a nucleic acid binding domain.” Thus, the vectors of claim 2 encode a recombinant binding moiety having a DNA binding domain and include a binding site for that DNA binding domain.

Ledley describes the use of recombinant DNA techniques to produce chimeric proteins having a DNA-binding domain and a receptor-binding domain, stating: “genetic sequences are constructed which encode the desired DNA-binding protein with a genetic element which will direct expression of the recombinant protein in a desired host.” Ledley, at page 10, lines 19-22. However, Ledley is devoid of any teaching of a vector that encodes a recombinant binding moiety having a DNA binding domain *and* includes a binding site for that DNA binding domain. *See, e.g.*, Figure 2 of Ledley, which discloses a complex between a vector and a DNA-binding protein that can also bind to a receptor. Whereas the vector of claim 2(2) encodes a binding moiety that can bind to this vector, the Ledley vector does not.

As Patten fails to remedy either of these deficiencies, the cited combination fails to teach or suggest at least two elements of claim 2.

#### Claims 14, 15 and 16

Claim 14 recites a “cell-specific recombinant binding moiety produced by expressing in a host cell a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2.” According to claim 2, this nucleic acid is derived from the recombination of at least two forms of “at least one nucleic acid which comprises a polynucleotide that encodes a nucleic acid binding domain.” Claim 14 further recites:

the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys3His (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV tat and HIV rev.

Claim 15 recites a “composition for eliciting an immune response that comprises the cell-specific binding moiety of claim 14” and thus incorporates the

requirement that the cell-specific binding moiety be obtained by the method employing the nucleic acid binding domain recited in claim 14. This element is also present in claim 16, which recites a “composition for eliciting an immune response that comprises a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2.”

None of the cited references teaches or suggests a cell-specific recombinant binding moiety like that obtained by the method of claim 2 that is derived from recombination of at least two forms of a nucleic acid which comprises a polynucleotide that encodes one of the recited nucleic acid binding domains. Notably, such a binding moiety would include a “a cell-specific ligand that specifically binds to a protein on the surface of a cell of interest” (*see* claim 2(1)) and a “a nucleic acid binding domain” capable of binding to the same binding site as the nucleic acid binding domains recited in claims 14 and 16 and incorporated by reference into claim 15 (*see* claim 2).

### **Claims 17 and 22**

Claim 17 relates to a composition for eliciting an immune response that comprises “a recombinant binding moiety that comprises a nucleic acid binding domain and a cell-specific binding ligand” and “a polynucleotide that is capable of expressing an antigen and that comprises a binding site, wherein the nucleic acid binding domain is capable of specifically binding to the binding site.” Claim 22 relates to a method for producing a composition for eliciting an immune response and recites a method comprising coating a polynucleotide that is capable of expressing an antigen “with a recombinant cell-specific binding moiety.”

Ledley describes “the use recombinant DNA-binding proteins bound to DNA for the purposes of gene transfer and somatic gene therapy.” Ledley, at page 6, lines 6-8. However, Ledley neither teaches nor suggests the use of a cell-specific binding moiety bound to a polynucleotide that is capable of expressing antigen. None of the cited references teaches or suggests coating a polynucleotide that is capable of expressing an antigen with a cell-specific binding moiety of any type or composition comprising such a polynucleotide and a cell-specific binding moiety.

### **Claim 18**

Like claim 2, claim 18 relates to a “method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake, efficacy, or specificity of a vaccine or antigen for a target cell.” Claim 18 recites:

recombining at least first and second forms of at least one nucleic acid that comprises ***a polynucleotide which encodes a binding moiety of an enterotoxin***, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids.

(Emphasis added.) The Examiner recognized that claim 18 recited the use of a polynucleotide encoding a binding moiety of an enterotoxin, but failed to identify any teaching or suggestion in the cited references that would lead one skilled in the art to perform the claimed method using such a polynucleotide. Applicants have been unable to find any such teaching or suggestion in the cited references. Accordingly, Applicants submit that the Examiner has not, and cannot, establish that the cited references provide all of the elements of claim 18.

#### **Additional Independent Claims**

Claims 51-58 were not previously considered because these claims were erroneously withdrawn from consideration. Of these, claims 51, 57, and 58 are independent (although claims 57 and 58 refer to elements of other claims by reference). Applicants wish to point out that these claims are free of the cited art.

In particular, claim 51 relates to a “method for producing and screening a recombinant cell-specific binding moiety polypeptide for an ability to increase uptake, efficacy, or specificity of a vaccine antigen for a target cell.” Claim 51 recites a final step of “fusing or linking the recombinant cell-specific binding moiety polypeptide to the vaccine antigen or coating the vaccine antigen with the recombinant cell-specific binding moiety polypeptide.” Claim 58 recites a “composition for eliciting an immune response . . . produced by the method of claim 51.” As discussed above with respect to claims 17 and 22, the cited references fail to teach or suggest anything regarding any type of complex between a cell-specific binding moiety polypeptide and a vaccine antigen.

Claim 57 relates to a “method for producing a composition for eliciting an immune response.” Claim 57 recites “coating an antigen with a recombinant cell-specific binding moiety polypeptide produced by the method of claim 51.” This claim is distinguished from the cited references for at least the reasons discussed above for claim 51.

#### **A Prima Facie Obviousness Has Not Been Established**

The foregoing makes it clear that the Examiner has not established how the cited references, whether taken alone or in combination, teach or suggest all elements of the independent claims.

In addition, the record is unclear with respect to how the cited references provide motivation for combining or modifying their teachings to arrive at the claimed invention. The Examiner contended that:

One having ordinary skill at the time of the invention would have been motivated to . . . [perform the claimed method and/or make the claimed compositions] because the generation of a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element for binding to DNA could facilitate the efficiency of gene transfer and the effects of a genetic vaccine vector comprising polynucleotide sequences containing a nucleic acid binding site and [encoding] an optimized recombinant binding moiety containing a nucleic acid binding domain and a cell specific ligand.

Office Action, at page 9-10. However, the Examiner does not specifically indicate where such motivation is found in the references. The Examiner's rationale fails to take into account the need for specific motivation for modifying the teachings of references, which is patently improper in light of Federal Circuit precedent. A recent Federal Circuit case emphasizes that the requirement for specific motivation for combining or, as in the present application, modifying references is to be applied rigorously. The court stated in *In Re Werner Kotzab*, 217 F.3d 1365; 2000 U.S. App. LEXIS 15504; 55 USPQ2d 1313 (Fed. Cir. 2000):

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." *Id.* (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. (BNA) 303, 313 (Fed. Cir. 1983)).

Most if not all inventions arise from a combination of old elements. See *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2D (BNA) 1453, 1457 (Fed. Cir. 1998). Thus, every element of a claimed invention may often be found in the prior art. See *id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. See *id.* ***Rather, to establish obviousness based on a combination of the elements***

*disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.* See *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2D (BNA) 1635, 1637 (Fed. Cir. 1998); *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. (BNA) 1125, 1127 (Fed. Cir. 1984). Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. See *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582, 37 U.S.P.Q.2D (BNA) 1314, 1318 (Fed. Cir. 1996).

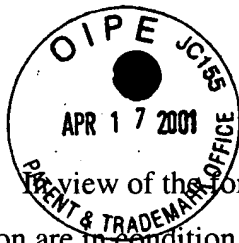
The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved. See *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617. *In addition, the teaching, motivation or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references.* See *WMS Gaming, Inc. v. International Game Tech.*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2D (BNA) 1385, 1397 (Fed. Cir. 1999). *The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.* See *In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. (BNA) 871, 881 (CCPA 1981) (and cases cited therein). *Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto.* See *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617. Broad conclusory statements standing alone are not "evidence." *Id.*

*In Re Werner Kotzab*, at 1369-1370 (emphasis added). The Federal Circuit further stated that *the particular finding required must explain why "the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."* *Id.* at 1371 (emphasis added). Applicants respectfully submit that the motivation cited by the Examiner fails to meet this standard.

Because the record fails to demonstrate that (1) the reference(s) teach or suggest all of the elements of the claimed invention and (2) that some motivation existed for combining or modifying the teachings of the references to arrive at the claimed invention, no *prima facie* case of obviousness has been established. Withdrawal of the rejection is therefore respectfully requested.



Conclusion

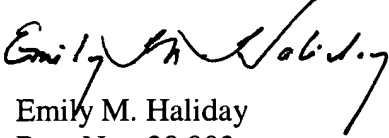


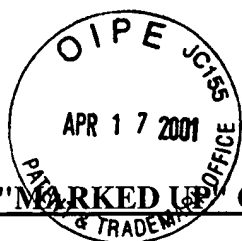
In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-8891.

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Respectfully submitted,

  
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Reg. No: 38,903



## APPENDIX A

### "MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF 09/247,866 WITH ENTRY OF THIS AMENDMENT

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1. (Amended) A method for [obtaining] producing and screening a cell-specific binding molecule [useful] for an ability to increase [increasing] uptake or specificity of a genetic vaccine for [to] a target cell, the method comprising:

creating a library of recombinant polynucleotides [that] by recombining at least one [a] nucleic acid that encodes a polypeptide that comprises a nucleic acid binding domain and at least one [a] nucleic acid that encodes a polypeptide that comprises a cell-specific binding domain; and

screening at least one member of the library for [to identify] a recombinant polynucleotide that encodes a binding molecule that can bind to a nucleic acid and to a cell-specific receptor.

2. (Amended) A method for [obtaining] producing and screening a recombinant cell-specific binding moiety [useful] for an ability to increase [increasing] uptake or specificity of a genetic vaccine for [to] a target cell, the method comprising:

(1) recombining at least first and second forms of at least one [a] nucleic acid which comprises a polynucleotide that encodes a nucleic acid binding domain and at least first and second forms of at least one [a] nucleic acid which comprises a polynucleotide that encodes a cell-specific ligand that specifically binds to a protein on the surface of a cell of interest, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant binding moiety-encoding nucleic acids;

(2) introducing [transfecting] into [a population of] one or more host cells [a] one or more members of a library of vectors, each of which comprises: a) a binding site specific for the nucleic acid binding domain and [2)] b) a member of the library of recombinant binding moiety-encoding nucleic acids, wherein the encoded recombinant binding moiety is expressed [and binds to the binding site to form a vector-binding moiety complex];

(3) [lysing the host cells under conditions that do not disrupt] binding the expressed recombinant binding moiety to a vector comprising the binding site to form a [of the] vector-binding moiety complex;

(4) contacting the vector-binding moiety complex with a target cell of interest; and

(5) determining if one or more [identifying] target cells [that] contain <sup>(a)</sup> vector, and recovering the [isolating the optimized] recombinant cell-specific binding moiety nucleic acid [acids] from any such [these] target cells.

3. (Amended) The method of claim 2, wherein the method further comprises:

(6) recombining at least one [optimized] recombinant binding moiety-encoding nucleic acid of (5) with a further form of the polynucleotide that encodes a nucleic acid binding domain and/or a further form of the polynucleotide that encodes a cell-specific ligand, which are the same or different from the first and second forms, to produce a further library of recombinant binding moiety-encoding nucleic acids;

(7) introducing [transfecting] into [a population of] one or more host cells [a] one or more members of a library of vectors, each of which [that] comprises: a) a binding site specific for the nucleic acid binding domain and [2)] b) a member of the further library of recombinant binding moiety-encoding nucleic acids, wherein the encoded recombinant binding moiety is expressed [and binds to the binding site to form a vector-binding moiety complex];

(8) [lysing the host cells under conditions that do not disrupt] binding the expressed recombinant binding moiety to a vector comprising the binding site to form a [of the] vector-binding moiety complex;

(9) contacting the vector-binding moiety complex with a target cell of interest and determining if one or more [identifying] target cells [that] contain <sup>(a)</sup> [the] vector; [and]

(10) recovering the [isolating the optimized] recombinant binding moiety nucleic acid [acids] from [the] any such target cells [which contain the vector]; and

(11) repeating (6) through (10) [, as necessary,] to screen for a [obtain a further optimized] cell-specific binding moiety useful for increasing uptake or specificity of a genetic vaccine vector for [to] a target cell.

4. (Amended) The method of claim 2, wherein the method [further] comprises screening for one or more [identifying] cell-specific binding moieties that increase uptake of a genetic vaccine vector by [result in the highest efficiency in transfecting] the target cells.

5. (Amended) The method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an *E. coli* CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys<sub>3</sub>His (SEQ ID NO:6) box.

7. (Amended) The method of claim 2, wherein the target cell of interest is selected from the group consisting of muscle cells, monocytes, dendritic cells, B cells, T cells, Langerhans cells, keratinocytes, [and] M-cells, liver cells and epithelial cells.

8. (Amended) The method of claim 7, wherein the target cell of interest is a professional antigen presenting cell.

10. (Amended) The method of claim 8, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40 ligand, fibrinogen, ICAM-1, Fc portion of immunoglobulin G, and a bacterial enterotoxin, or a subunit thereof.

12. (Amended) The method of claim 2, wherein [the] target cells that contain the vector are identified by selecting for expression of a selectable marker contained in the vector.

13. (Amended) The method of claim 2, wherein each [the optimized] recombinant binding moiety-encoding nucleic acid comprises a genetic vaccine vector.

14. (Amended) A cell-specific recombinant binding moiety produced by expressing in a host cell a [an optimized] recombinant binding moiety-encoding nucleic acid

obtained by the method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an *E. coli* CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys<sub>3</sub>His (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV *tat* and HIV *rev*.

15. (Amended) A composition for eliciting an immune response [genetic vaccine] that comprises a cell-specific recombinant binding moiety of claim 14.

16. (Amended) A composition for eliciting an immune response [genetic vaccine] that comprises a [an optimized] recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an *E. coli* CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys<sub>3</sub>His (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV *tat* and HIV *rev*.

17. (Amended) A composition for eliciting an immune response [genetic vaccine] that comprises:

- a) [an optimized] a recombinant binding moiety that comprises a nucleic acid binding domain and a cell-specific ligand, and
- b) a polynucleotide sequence that is capable of expressing an antigen comprises a binding site, wherein the nucleic acid binding domain is capable of specifically binding to the binding site.

18. (Twice Amended) A method for [obtaining] producing and screening a recombinant [an optimized] cell-specific binding moiety [useful] for an ability to increase

[increasing] uptake, efficacy, or specificity of a vaccine or antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one [a] nucleic acid that comprises a polynucleotide which encodes a binding moiety of an enterotoxin, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) introducing one or more members of [transfecting] a library of vectors, each of which comprises a member of the library of recombinant [that contain the library of] nucleic acids, into [a population of] one or more host cells, wherein the member of the library of recombinant nucleic acids is [are] expressed to form a recombinant cell-specific binding moiety polypeptide [polypeptides];

(3) contacting the recombinant cell-specific binding moiety polypeptide [polypeptides] with a cell surface receptor of a target cell; and

(4) determining if the [which] recombinant cell-specific binding moiety polypeptide [polypeptides] exhibits enhanced ability to bind to the target cell.

19. (Amended) The method of claim 18, wherein the cell surface receptor is present on the surface of a target cell during said contacting.

22. (Amended) A method for producing a composition for eliciting an immune response [enhancing uptake of a genetic vaccine vector by a target cell], the method comprising coating a polynucleotide that is capable of expressing an antigen [the genetic vaccine vector] with a [an optimized] recombinant cell-specific binding moiety produced by the method of claim 18.

23. The method of claim 18, wherein the recombinant cell-specific binding moiety polypeptide is [moieties are] expressed as a fusion protein on the surface of a replicable genetic package.

51. (Amended) A method for [obtaining] producing and screening a [an optimized] recombinant cell-specific binding moiety polypeptide [useful] for an ability to increase [increasing] uptake, efficacy, or specificity of a vaccine antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one [a] nucleic acid that comprises a polynucleotide which encodes a cell-specific binding moiety, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) introducing one or more members of a library of [transfecting] vectors, each of which comprises a member of the library of recombinant [that contain the library of] nucleic acids, into [a population of] one or more host cells, wherein the member of the library of recombinant nucleic acids is [are] expressed to form a recombinant cell-specific binding moiety polypeptide [polypeptides];

(3) contacting the recombinant cell-specific binding moiety polypeptide [polypeptides] with a cell surface receptor of a target cell; [and]

(4) determining if the [which] recombinant cell-specific binding moiety polypeptide [polypeptides] exhibits enhanced ability to bind to the target cell [to obtain an optimized recombinant cell-specific binding moiety polypeptide]; and

(5) fusing or linking the recombinant cell-specific binding moiety polypeptide to the vaccine antigen or coating the vaccine antigen with the recombinant cell-specific binding moiety polypeptide.

53. (Amended) The method of claim 51, wherein the [each] recombinant cell-specific binding moiety polypeptide is fused or linked to the vaccine antigen.

54. (Amended) The method of claim 51, wherein the target cell is selected from the group consisting of muscle cells, monocytes, dendritic cells, B cells, T cells, Langerhans cells, keratinocytes, M-cells, liver cells and epithelial cells.

55. (Amended) The method of claim 51, wherein the cell surface receptor is present on the surface of a target cell during said contacting.

56. (Amended) The method of claim 51, wherein the cell-specific binding moiety comprises a polypeptide derived from a protein selected from the group consisting of selected from the group consisting of CD2, CD28, CTLA-4, CD40, and ligands thereof; [,] fibrinogen; factor X; [,] ICAM-1;  $\beta$ -glycan; [,] Fc portion of immunoglobulin G; [,] and a bacterial enterotoxin, or a subunit thereof.

57. (Amended) A method for producing a composition for eliciting an immune response [enhancing uptake, efficacy, or specificity with which a vaccine antigen is taken up by a target cell], said method comprising coating an [the vaccine] antigen with a [an optimized] recombinant cell-specific binding moiety polypeptide produced by the method of claim 51.

58. (Amended) A composition for eliciting an immune response comprising an antigen and a recombinant cell-specific binding moiety polypeptide, wherein the composition is produced by the method of claim 51.

Added claims:

59. The method of claim 2, wherein the binding site of each vector is derived from a binding site present in at least one form of at least one nucleic acid of (1).

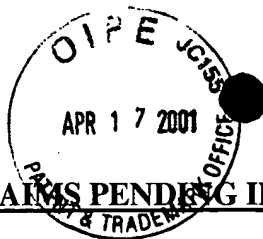
60. The method of claim 2, wherein the binding site is joined to the member of the library of recombinant binding moiety-encoding nucleic acids after said recombining.

61. The method of claim 2, wherein the vector-binding moiety complex forms inside the host cell and, prior to the contacting of (4), the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

62. The method of claim 3, wherein the vector-binding moiety complex of (8) forms inside the host cell and, prior to the contacting of (9), the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

63. The method of claim 2, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40, and ligands therefor; fibrinogen; factor X; ICAM-1;  $\beta$ -glycan; Fc portion of immunoglobulin G; and a bacterial enterotoxin, or a subunit thereof.

64. The method of claim 51, wherein the vaccine antigen is coated with the recombinant cell-specific binding moiety polypeptide.



## APPENDIX B

### CLAIMS PENDING IN USSN 09/247,866 WITH ENTRY OF THIS AMENDMENT

1. (Amended) A method for producing and screening a cell-specific binding molecule for an ability to increase uptake or specificity of a genetic vaccine for a target cell, the method comprising:

creating a library of recombinant polynucleotides by recombining at least one nucleic acid that encodes a polypeptide that comprises a nucleic acid binding domain and at least one nucleic acid that encodes a polypeptide that comprises a cell-specific binding domain; and

screening at least one member of the library for a recombinant polynucleotide that encodes a binding molecule that can bind to a nucleic acid and to a cell-specific receptor.

2. (Amended) A method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake or specificity of a genetic vaccine for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid which comprises a polynucleotide that encodes a nucleic acid binding domain and at least first and second forms of at least one nucleic acid which comprises a polynucleotide that encodes a cell-specific ligand that specifically binds to a protein on the surface of a cell of interest, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant binding moiety-encoding nucleic acids;

(2) introducing into one or more host cells one or more members of a library of vectors, each of which comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the library of recombinant binding moiety-encoding nucleic acids, wherein the encoded recombinant binding moiety is expressed;

(3) binding the expressed recombinant binding moiety to a vector comprising the binding site to form a vector-binding moiety complex;

(4) contacting the vector-binding moiety complex with a target cell of interest; and

(5) determining if one or more target cells contain a vector, and recovering the recombinant cell-specific binding moiety nucleic acid from any such target cells.

3. (Amended) The method of claim 2, wherein the method further comprises:

(6) recombining at least one recombinant binding moiety-encoding nucleic acid of (5) with a further form of the polynucleotide that encodes a nucleic acid binding domain and/or a further form of the polynucleotide that encodes a cell-specific ligand, which are the same or different from the first and second forms, to produce a further library of recombinant binding moiety-encoding nucleic acids;

(7) introducing into one or more host cells one or more members of a library of vectors, each of which comprises: a) a binding site specific for the nucleic acid binding domain and b) a member of the further library of recombinant binding moiety-encoding nucleic acids, wherein the encoded recombinant binding moiety is expressed;

(8) binding the expressed recombinant binding moiety to a vector comprising the binding site to form a vector-binding moiety complex;

(9) contacting the vector-binding moiety complex with a target cell of interest and determining if one or more target cells contain a vector;

(10) recovering the recombinant binding moiety nucleic acid from any such target cells; and

(11) repeating (6) through (10) to screen for a cell-specific binding moiety useful for increasing uptake or specificity of a genetic vaccine vector for a target cell.

4. (Amended) The method of claim 2, wherein the method comprises screening for one or more cell-specific binding moieties that increase uptake of a genetic vaccine vector by the target cells.

5. (Amended) The method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys3His (SEQ ID NO:6) box.

6. The method of claim 2, wherein the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV *tat* and HIV *rev*.

7. (Amended) The method of claim 2, wherein the target cell of interest is selected from the group consisting of muscle cells, monocytes, dendritic cells, B cells, T cells, Langerhans cells, keratinocytes, M-cells, liver cells and epithelial cells.

8. (Amended) The method of claim 7, wherein the target cell of interest is a professional antigen presenting cell.

9. The method of claim 8, wherein the antigen presenting cell is a dendritic cell, a monocyte/macrophage, a B cell, or a Langerhans cell. 10. (Amended) The method of claim 8, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40 ligand, fibrinogen, ICAM-1, Fc portion of immunoglobulin G, and a bacterial enterotoxin, or a subunit thereof.

10. (Amended) The method of claim 8, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40 ligand, fibrinogen, ICAM-1, Fc portion of immunoglobulin G, and a bacterial enterotoxin, or a subunit thereof.

11. The method of claim 2, wherein the target cell of interest is a human cell.

12. (Amended) The method of claim 2, wherein target cells that contain the vector are identified by selecting for expression of a selectable marker contained in the vector.

13. (Amended) The method of claim 2, wherein each recombinant binding moiety-encoding nucleic acid comprises a genetic vaccine vector.

14. (Amended) A cell-specific recombinant binding moiety produced by expressing in a host cell a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys3His (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV tat and HIV rev.

15. (Amended) A composition for eliciting an immune response that comprises a cell-specific recombinant binding moiety of claim 14.

16. (Amended) A composition for eliciting an immune response that comprises a recombinant binding moiety-encoding nucleic acid obtained by the method of claim 2, wherein the nucleic acid binding domain is a DNA binding domain derived from a protein selected from the group consisting of a transcriptional regulator, a polypeptide involved in DNA replication or recombination, a repressor, a histone, a protamine, an E. coli CAP protein, myc, a protein having a leucine zipper, a protein having a DNA binding basic domain, a protein having a POU domain, a protein having a zinc finger, and a protein having a Cys3His (SEQ ID NO:6) box or the nucleic acid binding domain is an RNA binding domain derived from a protein selected from the group consisting of HIV tat and HIV rev.

17. (Amended) A composition for eliciting an immune response that comprises:

a) a recombinant binding moiety that comprises a nucleic acid binding domain and a cell-specific ligand, and

b) a polynucleotide sequence that is capable of expressing an antigen comprises a binding site, wherein the nucleic acid binding domain is capable of specifically binding to the binding site.

18. (Twice Amended) A method for producing and screening a recombinant cell-specific binding moiety for an ability to increase uptake, efficacy, or specificity of a vaccine or antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid that comprises a polynucleotide which encodes a binding moiety of an enterotoxin, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) introducing one or more members of a library of vectors, each of which comprises a member of the library of recombinant nucleic acids, into one or more host cells, wherein the member of the library of recombinant nucleic acids is expressed to form a recombinant cell-specific binding moiety polypeptide;

(3) contacting the recombinant cell-specific binding moiety polypeptide with a cell surface receptor of a target cell; and

(4) determining if the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell.

19. (Amended) The method of claim 18, wherein the cell surface receptor is present on the surface of a target cell during said contacting.

20. The method of claim 18, wherein the cell surface receptor is  $G_{M1}$ .

21. The method of claim 18, wherein the host cell is a *V. cholerae* cell which is incapable of expressing CT-A.

22. (Amended) A method for producing a composition for eliciting an immune response, the method comprising coating a polynucleotide that is capable of expressing an antigen with a recombinant cell-specific binding moiety produced by the method of claim 18.

23. (Amended) The method of claim 18, wherein the recombinant cell-specific binding moiety polypeptide is expressed as a fusion protein on the surface of a replicable genetic package.

51. (Amended) A method for producing and screening a recombinant cell-specific binding moiety polypeptide for an ability to increase uptake, efficacy, or specificity of a vaccine antigen for a target cell, the method comprising:

(1) recombining at least first and second forms of at least one nucleic acid that comprises a polynucleotide which encodes a cell-specific binding moiety, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids;

(2) introducing one or more members of a library of vectors, each of which comprises a member of the library of recombinant nucleic acids, into one or more host cells, wherein the member of the library of recombinant nucleic acids is expressed to form a recombinant cell-specific binding moiety polypeptide;

(3) contacting the recombinant cell-specific binding moiety polypeptide with a cell surface receptor of a target cell;

(4) determining if the recombinant cell-specific binding moiety polypeptide exhibits enhanced ability to bind to the target cell; and

(5) fusing or linking the recombinant cell-specific binding moiety polypeptide to the vaccine antigen or coating the vaccine antigen with the recombinant cell-specific binding moiety polypeptide.

53. (Amended) The method of claim 51, wherein the recombinant cell-specific binding moiety polypeptide is fused or linked to the vaccine antigen.

54. (Amended) The method of claim 51, wherein the target cell is selected from the group consisting of muscle cells, monocytes, dendritic cells, B cells, T cells, Langerhans cells, keratinocytes, M-cells, liver cells and epithelial cells.

55. (Amended) The method of claim 51, wherein the cell surface receptor is present on the surface of a target cell during said contacting.

56. (Amended) The method of claim 51, wherein the cell-specific binding moiety comprises a polypeptide derived from a protein selected from the group consisting of selected from the group consisting of CD2, CD28, CTLA-4, CD40, and ligands thereof; fibrinogen; factor X; ICAM-1;  $\beta$ -glycan; Fc portion of immunoglobulin G; and a bacterial enterotoxin, or a subunit thereof.

57. (Amended) A method for producing a composition for eliciting an immune response, said method comprising coating an antigen with a recombinant cell-specific binding moiety polypeptide produced by the method of claim 51.

58. (Amended) A composition for eliciting an immune response comprising an antigen and a recombinant cell-specific binding moiety polypeptide, wherein the composition is produced by the method of claim 51.

59. The method of claim 2, wherein the binding site of each vector is derived from a binding site present in at least one form of at least one nucleic acid of (1).

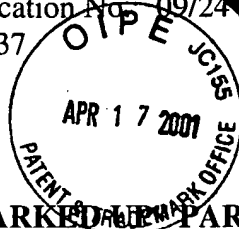
60. The method of claim 2, wherein the binding site is joined to the member of the library of recombinant binding moiety-encoding nucleic acids after said recombining.

61. The method of claim 2, wherein the vector-binding moiety complex forms inside the host cell and, prior to the contacting of (4), the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

62. The method of claim 3, wherein the vector-binding moiety complex of (8) forms inside the host cell and, prior to the contacting of (9), the host cell is lysed under conditions that do not disrupt the vector-binding moiety complex.

63. The method of claim 2, wherein the cell-specific ligand comprises a polypeptide derived from a protein selected from the group consisting of CD2, CD28, CTLA-4, CD40, and ligands thereof; fibrinogen; factor X; ICAM-1;  $\beta$ -glycan; Fc portion of immunoglobulin G; and a bacterial enterotoxin, or a subunit thereof.

64. The method of claim 51, wherein the vaccine antigen is coated with the recombinant cell-specific binding moiety polypeptide.



APPENDIX C

"MARKED UP" PARAGRAPHS ILLUSTRATING THE AMENDMENTS MADE TO THE  
SPECIFICATION OF 09/247,866 WITH ENTRY OF THIS AMENDMENT

1. Paragraph 1 on page 36:

DNA binding proteins which can be used in these methods include, but are not limited to, transcriptional regulators, enzymes involved in DNA replication (*e.g.*, *recA*) and recombination, and proteins that server structural functions on DNA (*e.g.*, histones, protamines). Other DNA binding proteins that can be used include the phage 434 repressor, the lambda phage cI and cro repressors, the *E. coli* CAP protein, myc, proteins with leucine zippers and DNA binding basic domains such as fos and jun; proteins with 'POU' domains such as the *Drosophila* paired protein; proteins with domains whose structures depend on metal ion chelation such as Cys<sub>2</sub>His<sub>2</sub> (SEQ ID NO: 4) zinc fingers found in TFIIIA, Zn<sub>2</sub>(Cys)<sub>6</sub> (SEQ ID NO: 5) cluster such as those found in yeast *Gal4*, the Cys<sub>3</sub> His (SEQ ID NO: 6) box found in retroviral nucleocapsid proteins, and the Zn<sub>2</sub>(Cys)<sub>8</sub> (SEQ ID NO: 7) clusters found in nuclear hormone receptor-type proteins; the phage P22 Arc and Mnt repressors (*see* Knight *et al.* (1989) *J. Biol. Chem.* 264: 3639-3642 and Bowie & Sauer (1989) *J. Biol. Chem.* 264: 7596-7602. RNA binding proteins are reviewed by Burd & Dreyfuss (1994) *Science* 265: 615-621, and include HIV Tat and Rev.